Articles

Children with Moderately Elevated Blood Lead Levels: A Role for Other Diagnostic Tests?

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In this study we examined potential limitations of relying exclusively on blood lead (BPb) levels to evaluate children with moderately elevated BPb levels (1.21–2.12 µmol/l, or 25–44 µg/dl). We tested the following hypotheses: 1) such children without elevated erythrocyte protoporphyrin (EP) levels (≥0.62 µmol/l or ≥35 µg/dl) are unlikely to respond to a chelating agent with a brisk urinary Pb diuresis; 2) those with elevated EP levels, but low hematologic indices consistent with iron deficiency, are also unlikely to respond to a chelating agent with a robust urinary Pb diuresis; and 3) those with elevated EP levels and iron sufficiency are more likely to respond to a chelating agent. To test these hypotheses, we performed retrospective analyses of the relationships between EP concentrations, hematologic indices, and urinary Pb excretion ratios (uPbr) in moderately Pb-poisoned children undergoing the CaNa₂EDTA lead mobilization test (Pb-MT). Data from 122 children were available. Urinary Pb excretion was limited in children with an EP <0.62 µmol/l (<35 µg/dl); only 5% (1/21) of Pb-MTs were positive (uPbr ≥0.6). In children with an EP ≥0.62 µmol/l, low hematologic indices, such as a mean corpuscular hemoglobin (MCH) <23 pg, were associated with relatively little Pb excretion (0/14 positive Pb-MTs). In contrast, 32% (28/87) of Pb-MTs were positive in children with an EP ≥0.62 µmol/l and iron sufficiency ($p<0.01$ by chi-square comparison between groups with EP ≥0.62 µmol/l and either MCH <23 pg or MCH ≥23 pg). We conclude that only a minority of moderately Pb-poisoned children will demonstrate enhanced urinary Pb excretion in response to chelation therapy. Some of the predicted nonresponders can be readily identified by adding the EP and complete blood count to the panel of tests performed. *Key words*: blood lead levels, chelation, erythrocyte protoporphyrin, iron deficiency, lead diagnosis, lead mobilization test, lead poisoning, urine lead.

The management of childhood lead poisoning has undergone considerable change since 1991 when the definition of Pb poisoning was lowered to a blood Pb (BPb) level ≥0.48 µmol/l (10 µg/dl). Universal screening of preschool children was recommended by both the Centers for Disease Control and Prevention and the American Academy of Pediatrics, while local epidemiologic data on the prevalence of lead poisoning accumulated (1,2).

Historically, erythrocyte protoporphyrin (EP) measurements were used for Pb screening purposes (3). This heme precursor accumulates in red (and other) cells in the presence of Pb or in the absence of sufficient iron (4). Increases in EP levels ≥0.62 µmol/l (≥35 µg/dl) are associated with elevated BPb levels, especially when BPb levels are ≥2.41 µmol/l (50 µg/dl); reportedly, only about 20% of children with BPb levels between 0.97 and 1.40 µmol/l (20–29 µg/dl) will have an EP ≥0.62 µmol/l (≥35 µg/dl) (5). The presence of an elevated EP level thus indicates the need for BPb and iron status determinations. However, because EP measurements fail to detect the majority of children with BPb values ≥0.48 µmol/l (10 µg/dl), the direct measurement of a BPb level has become the screening method of choice for childhood Pb poisoning (6).

Chelation therapy employs chemical agents to remove Pb from critical organs, thereby ameliorating further toxicity and potentially allowing for biochemical and general medical recovery. Their use is recommended for children with BPb levels ≥2.17 µmol/l (45 µg/dl) (1). For children with BPb levels 0.48–1.16 µmol/l (10–24 µg/dl), chelation therapy is not recommend except in clinical research protocols (1).

The indication for chelation therapy in moderately Pb-poisoned children (BPb 1.21–2.12 µmol/l or 25–44 µg/dl) has not been clearly defined. Approaches to such children have included nonselective chelation of all of them on the presumption of benefit, no chelation for any because of the absence of demonstrated long-term benefit, or selection for chelation based on further diagnostic testing. Nonspecific criteria, such as persistence of elevated BPb levels despite environmental intervention, have also been offered as justifications for this form of treatment, but without supporting evidence (7).

One diagnostic test that has been used in past decades for moderately Pb-poisoned children is the CaNa₂EDTA lead mobilization test (Pb-MT). This test examines the immediate responsiveness of the patient to a chelating agent, CaNa₂EDTA, in terms of urinary Pb excretion. Its historical development was predicated on the observation that workers in lead-based industries excreted larger amounts of Pb in response to this drug than nonexposed workers, despite comparable BPb levels; this responsiveness appeared to be related to the duration of exposure (8). The Pb-MT highlighted the limitations of relying solely on BPb level determinations as the predictor of the amount of Pb in other body compartments. The later development of bone Pb measurements by L-X-ray fluorescence in diverse populations confirmed this limitation of BPb (8). The Pb-MT was later adapted for children (9). A significant or positive Pb-MT was defined, in part, by a level of induced Pb excretion greater than the amount the child could or would excrete spontaneously. Because chelation-induced urinary lead excretion is comparable for the first 5 days of treatment, a positive Pb-MT is a predictor of responsiveness, in terms of Pb excretion, to a full 5-day course of treatment with the same drug (10).

Practical and theoretical considerations, however, have limited the utility, availability, and possible advisability of the Pb-MT. In particular, it requires parenteral administration of a drug and a timed urine collection of at least 6 and preferably 8 hr (11,12). An unreplicated study found transient, but not sustained, elevations in brain Pb content after single dose injections of CaNa₂EDTA given to leaded rats (13). No clinical correlates to this study have been described in humans. Finally, whether children chelated on the basis of this test have better outcomes has also not been examined.

Thus, the BPb level has become the sole biochemical determinant for clinical management. In this study we have examined potential limitations of relying exclusively on BPb levels to determine the need for chelation therapy in children with moderately elevated BPb levels. In particular, we explored the heterogeneity in the population of children defined by comparable BPb levels. We attempted to define subgroups of such children by combining measures of Pb exposure (BPb), toxicity (EP), and drug responsiveness (Pb-MT). We tested the following

hypotheses: 1) children with moderately elevated BPb levels but low EP levels (<0.62 µmol/l or <35 µg/dl) are unlikely to have a Pb diuresis in response to CaNa$_2$EDTA; 2) a subset of patients with elevated BPb and EP levels, the latter measure high as the result of iron deficiency rather than Pb poisoning, will not respond to this chelating agent with a urinary Pb diuresis; and 3) children with elevated BPb and EP levels, but without evidence of iron deficiency, are more likely to have accumulated Pb stores and are more likely to respond to a chelating agent with a Pb diuresis.

Methods

We performed a retrospective analysis of data obtained from children who completed Pb-MTs over an 18-month period (March 1992–October 1993). The children were referred to our lead clinic in the Bronx, New York, for the evaluation of a screening BPb level of 1.21–2.12 µmol/l. Case selection began after BPb replaced EP as the recommended screening method to detect childhood Pb poisoning (1). Nonetheless, our laboratory continued to measure EP levels in children who had BPb values ≥1.21 µmol/l. The children were between 1 and 6 years of age.

The Pb-MT protocol we used was as follows. We began by obtaining a blood sample for later BPb and EP determinations on the day of the test. A single dose of CaNa$_2$EDTA (500 mg/m^2), mixed 1:1 by volume with 1% procaine, was administered in the quadriceps (alternatively, the drug without procaine can be given intravenously). This marked the beginning of an 8-hr urine collection period for later Pb determination (9,11). Urine Pb content (uPb; in micrograms) was divided by the dose of CaNa$_2$EDTA given (in milligrams) to yield the uPb/CaNa$_2$EDTA ratio (uPbr). A ratio ≥0.6 is considered a significant Pb diuresis (a positive test) and indicates the need for further chelation therapy (14).

As indirect measures of iron sufficiency, a blood sample for complete blood count (CBC) analysis was also obtained within 1 month prior to the Pb-MT. Measures on the CBC were the hematocrit (Hct), hemoglobin (Hgb), mean corpuscular volume (MCV), and mean corpuscular hemoglobin (MCH).

Blood and urine Pb were measured by graphite furnace atomic absorption spectrometry; the 95% confidence limits of the methods are 0.048 µmol/l (1 µg/dl) and 0.241 µmol/volume (5 µg/volume), respectively (10). EP was measured by the ethyl-acetate–acetic acid extraction method (4). The CBC was measured on an automated instrument (Cell-Dyn 900, Sequoia Turner).

Data analyses included inspection of the data to determine cutoffs of predictors of the Pb-MT. Statistical techniques included chi-square and regression analyses, with uPbr as the dependent variable. For the regression analyses, a stepwise approach was used. Because of significant skew and kurtosis in its distribution, the log of EP was used in the statistical analyses.

Results

Complete data from 122 children were available for analyses. Ninety percent.of the children were Hispanic or African American; 85% received Medicaid or were self-paying.

Only mean uPbr and the percentage of positive Pb-MTs (uPbr ≥0.6) were significantly different between the high and low EP groups (Table 1). Inspection of the distributions of uPbr versus BPb or age did not provide clinically useful information, i.e., cutoffs predictive of a negative Pb-MT. The distribution of uPbr results by levels of EP, MCH, MCV, Hgb, and, to a lesser extent, Hct are noteworthy, as shown for EP and MCH in Figure 1 (similar plots for uPbr versus MCV, Hgb, and Hct are available on request). Twenty-one of the 122 children (17.2%) had EP levels <0.62 µmol/l (<35 µg/dl) on the day of testing (Table 2). Of these, only one had a uPbr ≥0.6 (4.8%) (Fig. 1, Table 2). In contrast, 28 of the 101 Pb-MTs performed in children with elevated EP levels were positive (27.7%). The difference in the proportion of positive and negative Pb-MTs (i.e., uPbr ≥0.6 and <0.6, respectively) in the two EP groups (EP ≥0.62 µmol/l and <0.62 µmol/l, respectively) was significant by chi-square analysis (p<0.05).

The distribution of Pb-MT results by MCH is also shown in Figure 1. Inspection of these data revealed a distinct group characterized by an MCH <23 pg; no members of this group had a positive Pb-MT (0/18). In contrast, 29 of 104 Pb-MTs performed in children with an MCH ≥23 pg were positive (27.9%; p<0.05).

When the uPbr data are grouped by EP and MCH (Table 2), it is evident that low values of either alone is predictive of a negative Pb-MT. Only if both EP and MCH are elevated does uPbr become unpredictable. Similar results are obtained using the other hematological indices (analyses not shown). The Pb-MT was unlikely to be positive if the MCV was ≤70 fl, the Hct was ≤30%, or the Hgb was ≤106 g/l. As with MCH and EP, these factors identify overlapping, but not identical, groups of children with very low likelihood of having positive Pb-MTs. Thus, having a low (below cutoff) value on any of these measures (EP, MCH, MCV, Hgb, Hct) was associated with a low uPbr (<0.6).

BPb, age, EP, and MCH were significantly correlated with uPbr in bivariate analyses (Table 3). To determine whether these four correlates of uPbr accounted independently for part of the variance in uPbr, we evaluated a series of multiple regression models that included these variables, as well as MCV, Hgb, and HCT (forward stepwise regression). We found that only age, BPb, EP, and MCH significantly contributed to the models without interactions (Table 3). Together they accounted for 30% of the variance in uPbr.

Because red cell indices are lower in African-American than in other American children and 45% of the children in this group were African-American, we examined the effect of race on Pb-MT outcomes (15). There were no significant differences in the percentage of children with high or low indices. The percentage of positive Pb-MTs were 27% and 24% in the African-American and non-African-American (mainly Hispanic) children, respectively (p>0.05 by chi-square test).

Discussion

Just under 1% of the children screened for Pb poisoning in the catchment area of our medical center during the early 1990s (primarily the Bronx and lower Westchester counties) have BPb levels ≥1.21 µmol/l (25 µg/dl). An additional 8% have BPb levels between 0.48 and 1.21 µmol/l (10–25 µg/dl). Our Pb clinic patients have the characteristics of a population most at risk for childhood Pb poisoning: it is composed primarily of minority (Hispanic and African-American) children who live in the inner city, have a low income level, and live in housing built before 1960 (16).

Clinical interventions for these children should include identification and eradication

Table 1. Results by erythrocyte protoporphyrin (EP) category

Variable	EP<35 µg/dl[a] (n = 21)	EP≥35 µg/dl[a] (n = 101)
Age (years)	3.4 ± 1.2	3.4 ± 1.5
BPb[b] (µg/dl)	31 ± 4	32 ± 6
uPbr	0.31 ± 0.13	0.49 ± 0.26*
Hgb (g/l)	121 ± 11	120 ± 11
Hct (%)	36 ± 3	35 ± 3
MCV (fl)	74 ± 8	75 ± 7
MCH (pg)	25 ± 3	26 ± 3
(+) Pb-MT [n (%)]	1 (5%)	28 (28%)*

Abbreviations: BPb, blood lead; uPbr, urinary lead to CaNa$_2$EDTA dose ratio; Hgb, hemoglobin; Hct, hematocrit; MCV, mean corpuscular volume; MCH, mean corpuscular hemoglogin; Pb-MT, lead mobilization test. Values are given as mean ± standard deviation except for Pb-MT.
[a]To convert to µmol/l, multiply by 0.0177.
[b]To convert to µmol/l, multiply by 0.0483.
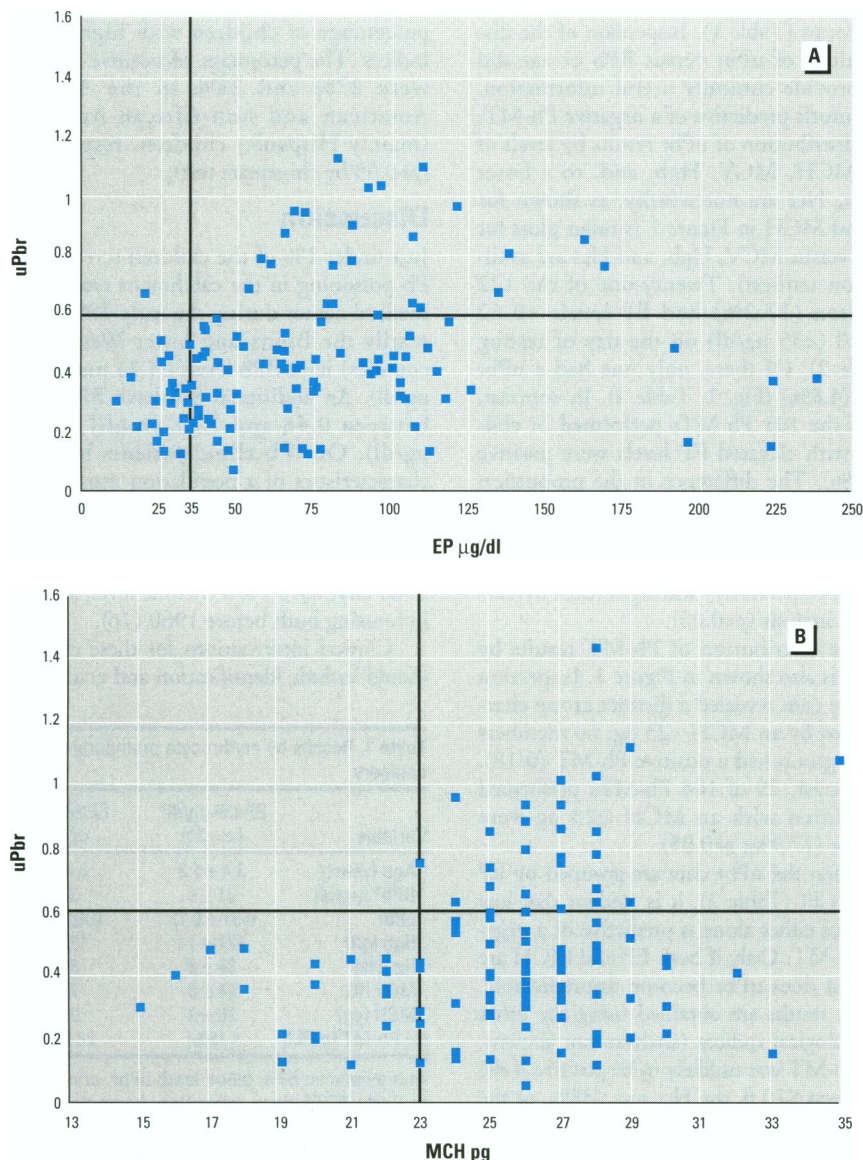*p<0.05; between group comparisons by *t*-test or chi-square.

of the environmental Pb source, nutritional information and supplementation with essential minerals (as indicated), and the possibility of chelation. Selection for chelation therapy has been based on provider preference (17). Those who believe that moderately elevated BPb levels are highly associated with the risk of neurotoxicity and therefore should be reduced promptly offer chelation in the hope that it will be successful at removing Pb expeditiously. Historically, chelation with parenterally administered medications was provided in the hospital. Chelation may have become more acceptable to some providers with the availability of the orally administered drug dimercaptosuccinic acid (succimer). This

drug is at least as capable as $CaNa_2EDTA$ at lowering BPb levels over 5-day treatment periods when comparable dosage is administered, determined on a per meter squared basis (succimer at 1,050 mg/m²/day, not at 30 mg/kg/day as recommended by the drug company in its inserts, because the recommended dose results in undertreatment in children; the larger succimer dose is comparable to $CaNa_2EDTA$ at 1,000 mg/m²/day) (18,19). However, a rebound in BPb levels occurs after cessation of treatment with either drug. In addition, transient toxicities have occurred during succimer use, and the drug increases intestinal Pb absorption in normal humans (20). Other providers, citing the lack of controlled studies that

demonstrate either a sustained effect of chelation therapy in asymptomatic, moderately Pb-poisoned children on BPb levels or neurobehavioral outcomes, have refrained from offering any drug treatment.

In this study, we postulated that EP levels, as a marker of Pb toxicity that lags weeks behind the increase in BPb levels after ingestion, may help identify children for chelation therapy. Children with high EP levels due to Pb poisoning would excrete more Pb; children with low EP levels, indicating a smaller body burden of Pb or recent exposure, would excrete less Pb. Our results support these hypotheses: children with low EP values were unlikely to excrete significant amounts of Pb when given a test dose of a chelating agent. In contrast, children with high EP levels were much more likely to excrete large amounts of Pb.

Because an elevated EP level may be due to iron deficiency as well as to Pb poisoning, we then examined red cell indices obtained prior to the Pb-MT as indirect measures of iron status (21). We found that low MCH, MCV, or Hgb levels, which are consistent with but not diagnostic of Fe

Table 2. Lead mobilization test (Pb-MT) results by erthrocyte protoporphyrin (EP) and mean corpuscular hemoglobin (MCH)

EP (μg/dl)[a]	MCH (pg)	Total (n)	Pb-MT (-) (n)	Pb-MT (+) (n)
<35	<23	4	4	0*
	≥23	17	16	1*
≥35	<23	14	14	0*
	≥23	87	59	28*

[a]To convert to μmol/l, multiply by 0.0177.
*p<0.05 between group comparisons for EP>35 versus EP≥35 μg/dl and for MCH<23 versus MCH ≥23 pg.

Table 3. Correlations with urinary Pb to $CaNa_2EDTA$ dose ratio

Variable	Bivariate Correlation coefficient	Bivariate p-value	Multivariate Standardized coefficient	Multivariate p-value
Age	0.336	0.000	0.332	0.000
BPb	0.236	0.009	0.191	0.020
EP	0.343	0.000	0.332	0.000
MCH	0.234	0.009	0.157	0.054
MCV	0.153	0.092		
Hct	-0.091	0.321		
Hgb	0.045	0.623		

Abbreviations: BPb, blood lead; EP, erythrocyte protoporphyrin; MCH, mean corpuscular hemoglobin; MCV, mean corpuscular volume; Hct, hematocrit; Hgb, hemoglobin. The significance levels of the bivariate correlations are uncorrected for multiple tests. The standardized coefficients and p-values of the significant variables in the final multivariate model derived from forward stepwise regression analyses are shown in the columns on the right.

Figure 1. (A) The relationship between erythrocyte protoporphyrin (EP) and lead mobilization test (Pb-MT) results expressed as uPbr. The vertical bar at 35 μg/dl indicates the current definition for an elevated EP level; the horizontal bar at 0.6 represents the cutoff for the Pb-MT. Two cases are not shown: EP= 299, uPbr = 0.75; and EP = 424, uPbr = 0.74. (B) The relationship between mean corpuscular volume (MCH) and Pb-MT results expressed as uPbr. The bar at 23 pg indicates the cutoff for MCH that best predicts the Pb-MT.

deficiency, were associated with low urinary Pb excretion. This supports our second hypothesis, namely, that a subset of children with both elevated BPb and EP levels and biochemical evidence consistent with Fe deficiency will excrete less Pb. In this regard, we have reported previously that children with low ferritin levels excreted less Pb during the Pb-MT, despite comparable BPb levels at the time of testing (22). These hematologic measures are not independent predictors of uPbr, as shown in the regression analyses, and measurement of MCH should suffice for the purpose of predicting Pb-MT outcomes. We did not determine in this study whether the failure to induce a Pb diuresis in these children was due to lower body stores of Pb, a lack of efficacy of drug in the presence of Fe deficiency, or that low CBC indices per se affect or reflect Pb availability to a chelating agent independent of Fe deficiency.

In this group, age was independently and positively related to uPbr. We speculate that age was a surrogate for duration of Pb exposure prior to enrollment at the clinic.

Stratifying by BPb and then by EP did not markedly improve predictability of uPbr. For example, although 100% of our children with BPb ≥1.94 μmol/l (40 μg/dl) had elevated EP levels, only 47% were Pb-MT positive. Thus, BPb by itself was not a good predictor of uPbr in this limited BPb range. This is consistent with our previous studies (10). The high percentage of elevated EP levels in this study group probably reflects the period of transition from its use as the screening tool of choice to direct BPb measurements.

Moderately elevated BPb levels indicate absorption of Pb, but do not necessarily predict the total amount of Pb accumulated in the body, the susceptibility of the individual child to a given amount of Pb, or the ability of chelating agents to enhance Pb excretion (22–24). Other diagnostic methods such as bone Pb measurements by X-ray fluorescence (XRF), EP level determinations, and the Pb-MT address some of these issues more directly (6,25,26). The XRF techniques, L-XRF and K-XRF, are noninvasive methods for measuring cortical (L-XRF) and trabecular (K-XRF) bone Pb content. L-XRF methodology has been used extensively in young children (8,25,26); comparison of bone Pb measurements and Pb-MT results in children with BPb levels between 1.21 and 2.66 μmol/l (25–55 μg/dl) yielded a correlation coefficient of 0.472 (p<0.001), which was somewhat less than the correlation between BPb and Pb-MT of 0.701 in the same children (25). At present, XRF methodologies are available only at a few research centers nationally. In general, the

Pb-MT is a difficult test to perform in very young children in other than expert settings. In contrast, the EP test is readily available from commercial laboratories and can be obtained from the same blood sample drawn for BPb determination. Ultimately, selection of children for chelation therapy should be based on the results of randomized controlled studies showing efficacy of chelation at removing Pb and improving measures of Pb-induced toxicity, or at least the cessation of further toxic events. These studies have yet to be completed in children with moderately elevated BPb levels.

The Pb-MT has become a controversial diagnostic tool, with few proponents for its clinical use (7). Objections to the difficulty in its execution, its cost, and concern about redistribution of internal stores of Pb have diminished its use. In addition, its clinical relevance is unknown because improvements in neurobehavioral outcomes based on Pb-MT-determined courses of chelation therapy have not been studied to date (27).

Nevertheless, long experience with the use of the Pb-MT points out a therapeutic dilemma: groups of children with comparable BPb levels can have significantly different amounts of Pb in their bodies and different susceptibility to that Pb which has accumulated. Clearly, those children whose BPb levels are due to recent ingestion without Pb accumulation or evidence of toxicity are least likely to benefit from drug treatment, if at all. How do we differentiate these children from those with longer term exposure, accumulation, and toxicity? Taking an environmental history may help determine duration of exposure, but does not quantify ingestion or body burden. In contrast, uPbr in response to the CaNa$_2$EDTA Pb-MT is correlated with bone Pb levels, and bone is the major reservoir of Pb (25). Previous work has shown that bone Pb is mobilized by CaNa$_2$EDTA (26,28,29). In the current study, the uPbr was also associated with a measure of Pb related toxicity, the EP level. Thus, children with elevated bone Pb stores and Pb-related toxicity (high EP levels) are more likely to excrete greater amounts of Pb in response to a test dose of CaNa$_2$EDTA (greater uPbr).

The criteria for interpreting an 8-hr Pb-MT were derived from a previous 24-hr version of the test in which a full day's dose of CaNa$_2$EDTA was administered (11). Furthermore, urinary Pb excretion on the first day of a course of chelation therapy is a predictor of urinary Pb excretion throughout the course (18,19). The Pb-MT therefore gives some indication of Pb burden beyond the blood compartment, is associated with a measure of toxicity, and directly predicts whether children will excrete Pb at an enhanced rate in response to drug treat-

ment with CaNa$_2$EDTA and, probably, succimer. It appears reasonable that children who do not excrete much Pb during the Pb-MT will not excrete much Pb during a full course of chelation; as a corollary, these children will not have a reduction in their body burdens of Pb, although they may show a decline in BPb levels.

In this sense, the Pb-MT is a useful tool for differentiating groups of children with moderately elevated BPb levels as to their expected responsiveness to chelation-induced Pb excretion. What it does not provide at the present time, even in children who are large Pb excreters, is a prediction of clinical outcomes, such as improvement in cognitive test scores after chelation therapy (27). Unfortunately, there are no publications of studies that have used randomized controlled designs to test chelation efficacy for children with moderately elevated BPb levels (with or without the Pb-MT), if long-term outcomes on cognitive measures are used as the gold standard.

In summary, in children with moderately elevated BPb levels, the EP and CBC indices are particularly useful adjuncts in predicting responsiveness to the chelating agent CaNa$_2$EDTA. This observation can probably be extended to treatment with succimer because children with comparably elevated BPb levels excrete similar amounts of Pb daily, whether treated with CaNa$_2$EDTA or appropriate doses of succimer (18,19). Children with either an EP <0.62 μmol/l (<35 μg/dl), an MCH <23 pg, an MCV <70 fl, or an Hgb <106 g/l are very unlikely to respond to drug treatment with Pb diuresis. We do not recommend chelation therapy in such children until future studies demonstrate clinical efficacy. Fe therapy should be initiated for those with indices consistent with Fe deficiency. Because most Pb-poisoned children with elevated EP levels and CBC indices above the thresholds defined in this paper still have negative Pb-MT results, further diagnostic evaluation appears to be warranted prior to the initiation of chelation therapy. These evaluations may include the Pb-MT, bone Pb measurement, or repeatedly elevated blood Pb and EP analyses.

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